Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications

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Ritonavir, a strong cytochrome P450 (CYP) 3A4 inhibitor and a P-glycoprotein inhibitor, is coadministered with nirmatrelvir to increase the blood concentration of nirmatrelvir, thereby making it effective against SARS-CoV-2. Ritonavir may also increase blood concentrations of certain concomitant medications. Because ritonavir-boosted nirmatrelvir (Paxlovid) is the only highly effective oral antiviral for the treatment of COVID-19, drug interactions that can be safely managed should not preclude the use of this medication.

Clinicians should be aware that many commonly used medications can be safely coadministered with ritonavir-boosted nirmatrelvir despite its drug-drug interaction potential. Box 1 includes commonly prescribed medications that are not expected to have clinically relevant interactions with ritonavir-boosted nirmatrelvir.

Box 1. Commonly Prescribed Outpatient Medications Not Expected to Have Clinically Relevant Interactions With Ritonavir-Boosted Nirmatrelvir (Paxlovid)

Medications Without Clinically Relevant Interactions

These commonly prescribed medications may be coadministered without dose adjustment and without increased monitoring.[a] This list is not inclusive of all noninteracting medications within each drug category.

Acid reducing agents
- Famotidine
- Omeprazole
- Pantoprazole

Allergy medications
- Cetirizine
- Diphenhydramine
- Loratadine

Anti-infective agents
- Azithromycin
- Hydroxychloroquine

Cardiovascular agents
- Aspirin
- Atenolol
- Carvedilol
- Furosemide
- Hydrochlorothiazide
- Irbesartan
- Isosorbide Dinitrate
- Lisinopril
- Losartan
- Metoprolol
- Prasugrel

Diabetes medications
- Empagliflozin
- Insulin
- Metformin
- Pioglitazone

Immunosuppressants
- Methotrexate
- Mycophenolate
- Prednisone

Lipid-modifying agents
- Ezetimibe
- Pitavastatin
- Pravastatin

Neuropsychiatric agents
- Amitriptyline
- Bupropion
- Citalopram
- Duloxetine
- Escitalopram
- Fluoxetine
- Gabapentin
- Lorazepam
- Nortriptyline
- Olanzapine
- Paroxetine
- Sertraline
- Venlafaxine

Pain medications
- Acetaminophen
- Aspirin
- Codeine
- Ibuprofen
- Naproxen

Respiratory medications
- Corticosteroids (inhaled)
- Formoterol
- Montelukast

Miscellaneous
- Allopurinol
- Contraceptives (oral)[b]
- Donepezil
- Enoxaparin
- Finasteride
- Levothyroxine
- Ondansetron

Medications Without Clinically Relevant Interactions, continued

[a] This list is primarily based on the most common medication searches by U.S. users on the Liverpool COVID-19 Drug Interactions website between January 1 and April 13, 2022 (internal communication, April 2022). The Liverpool website classifies these medications as those that have no interaction or weak interaction with ritonavir-boosted nirmatrelvir.

[b] The Food and Drug Administration Emergency Use Authorization for ritonavir-boosted nirmatrelvir suggests that individuals who use contraceptive products containing ethinyl estradiol consider using a backup, nonhormonal contraceptive method because coadministration may result in low ethinyl estradiol levels. However, the low level is not expected to be clinically significant during 5 days of therapy. The progestin concentration of a combined hormonal contraceptive is expected to remain similar or increase with coadministration, which would maintain the effectiveness of the oral contraceptive.

Medications That Have Clinically Relevant Drug-Drug Interactions With Ritonavir-Boosted Nirmatrelvir

Clinicians should be aware that, in some cases, drug-drug interactions with ritonavir-boosted nirmatrelvir may lead to serious or life-threatening drug toxicities. The recommended treatment course of ritonavir-boosted nirmatrelvir for COVID-19 is 5 days. After the last dose is administered, most of the interaction potential resolves within 2 to 3 days, although resolution may take longer in elderly adults.[1]

Ritonavir-boosted nirmatrelvir should not be given within 2 weeks of administering a strong CYP3A4 inducer (e.g., St. John's wort, rifampin). Ritonavir-boosted nirmatrelvir is **contraindicated** in this setting, because strong CYP3A4 inducers may reduce the concentrations of nirmatrelvir and ritonavir, rendering the treatment ineffective against SARS-CoV-2. Alternative treatment for COVID-19 should be prescribed.

Identifying Drug-Drug Interactions

Before prescribing ritonavir-boosted nirmatrelvir, carefully review the patient's concomitant medications, including over-the-counter medicines, herbal supplements, and recreational drugs.

Consult 1 or more of the following resources for information on identifying and managing drug-drug interactions:

- Quick reference lists:
  - Box 1 lists commonly prescribed outpatient medications that are not expected to have clinically relevant interactions with ritonavir-boosted nirmatrelvir.
  - Box 2 lists medications that have clinically relevant drug-drug interactions with ritonavir-boosted nirmatrelvir.
- Web-based drug-drug interaction checker:
  - The Liverpool COVID-19 Drug Interactions website
- Tables with guidance on managing specific drug-drug interactions:
  - The Ontario COVID-19 Science Advisory Table
  - The Food and Drug Administration Emergency Use Authorization fact sheet and checklist for ritonavir-boosted nirmatrelvir

Consider expert consultation (e.g., with a pharmacist, an HIV specialist, or the patient's specialist providers), especially for patients receiving highly specialized therapies or drugs prone to concentration-dependent toxicities, such as certain anticonvulsant, anticoagulant, antiarrhythmic, chemotherapeutic, neuropsychiatric, and immunosuppressant drugs.

Management Strategies for Drug-Drug Interactions

Consider the magnitude and significance of the potential interaction when choosing management strategies for patients who are to receive ritonavir-boosted nirmatrelvir. Potential strategies include:

- Temporarily withholding the concomitant medication,
- Increasing monitoring for potential adverse reactions to the concomitant medication,
- Adjusting the dose of the concomitant medication,
- Using an alternative to the concomitant medication, *or*
- Using alternative COVID-19 therapies (see Therapeutic Management of Nonhospitalized Adults With COVID-19).

Use the chosen strategy for the 5-day duration of ritonavir-boosted nirmatrelvir treatment and for at least 2 to 3 days after treatment completion. The strategy may need to continue for a longer duration if ritonavir-boosted nirmatrelvir is initiated in an elderly patient or if the interacting medication has a long half-life.

Box 2. Outpatient Medications That Have Clinically Relevant Drug-Drug Interactions With Ritonavir-Boosted Nirmatrelvir (Paxlovid)

Not all medications that may interact with ritonavir-boosted nirmatrelvir are included in Box 2. Deviation from the recommended strategies may be appropriate in certain clinical scenarios.

<table>
<tr><th colspan="3">Prescribe Alternative COVID-19 Therapy</th></tr>
<tr><td colspan="3">For these medications, management strategies are not possible or feasible, or the risks outweigh the potential benefits.</td></tr>
<tr><td>Anticonvulsants
• Carbamazepine
• Phenobarbital
• Phenytoin
• Primidone
Anti-infective agents
• Glecaprevir/pibrentasvir
• Rifampin
• Rifapentine
Immunosuppressants
• Voclosporin</td><td>Cardiovascular agents
• Amiodarone
• Clopidogrel[a,b]
• Disopyramide
• Dofetilide
• Dronedarone
• Eplerenone
• Flecainide
• Ivabradine
• Propafenone
• Quinidine
Neuropsychiatric agents
• Clozapine
• Lumateperone
• Lurasidone
• Midazolam (oral)
• Pimozide</td><td>Pain medications
• Meperidine (pethidine)
Pulmonary hypertension medications
• Sildenafil
• Tadalafil
• Vardenafil
Miscellaneous
• Bosentan
• Certain chemotherapeutic agents[c]
• Ergot derivatives
• Lumacaftor/ivacaftor
• St. John’s wort
• Tolvaptan</td></tr>
</table>

Temporarily Withhold Concomitant Medication, If Clinically Appropriate

Withhold these medications during ritonavir-boosted nirmatrelvir treatment and for at least 2–3 days after treatment completion. They may need to be withheld for longer if the patient is elderly or the medication has a long half-life. If withholding is not clinically appropriate, use an alternative concomitant medication or COVID-19 therapy.

Anticoagulants
- Rivaroxaban[d]

Anti-infective agents
- Erythromycin

BPH medications
- Alfuzosin
- Silodosin

Cardiovascular agents
- Aliskiren
- Ranolazine
- Ticagrelor[b]
- Vorapaxar

Immunosuppressants[f]
- Everolimus
- Sirolimus
- Tacrolimus

Lipid-modifying agents
- Atorvastatin[e]
- Lomitapide
- Lovastatin[e]
- Rosuvastatin[e]
- Simvastatin[e]

Migraine medications
- Eletriptan
- Rimegepant
- Ubrogepant

Neuropsychiatric agents
- Clonazepam[g]
- Clorazepate[g]
- Diazepam[g]
- Estazolam[g]
- Flurazepam[g]
- Suvorexant
- Triazolam[g]

Erectile dysfunction medications
- Avanafil

Respiratory medications
- Salmeterol

Miscellaneous
- Certain chemotherapeutic agents[c]
- Colchicine[h]
- Finerenone
- Flibanserin
- Naloxegol

Adjust Concomitant Medication Dose and Monitor for Adverse Effects

Consult the Liverpool COVID-19 Drug Interactions website or the Ontario COVID-19 Science Advisory Table for specific dosing recommendations.[i] If the dose of the concomitant medication cannot be adjusted, withhold the medication (if clinically appropriate) or use an alternative concomitant medication or COVID-19 therapy.

Anticoagulants
- Apixaban
- Dabigatran
- Edoxaban

Anti-infective agents
- Clarithromycin
- Itraconazole
- Ketoconazole
- Maraviroc
- Rifabutin

BPH medications
- Tamsulosin

Cardiovascular agents
- Cilostazol
- Digoxin
- Mexiletine

Diabetes medications
- Saxagliptin

Erectile dysfunction medications
- Sildenafil
- Tadalafil
- Vardenafil

Immunosuppressants[f]
- Cyclosporine

Neuropsychiatric agents
- Alprazolam[g]
- Aripiprazole
- Brexpiprazole
- Buspirone
- Cariprazine
- Chlordiazepoxide[g]
- Clobazam[g]
- Iloperidone
- Pimavanserin
- Quetiapine
- Trazodone

Pain medications
- Fentanyl
- Hydrocodone
- Oxycodone

Pulmonary hypertension medications
- Riociguat

Miscellaneous
- Certain chemotherapeutic agents[c]
- Darifenacin
- Elexacaftor/tezacaftor/ivacaftor
- Eluxadoline
- Ivacaftor
- Tezacaftor/ivacaftor

Continue Concomitant Medication and Monitor for Adverse Effects		
Pre-emptive dose adjustment is not required but may be considered. Educate patients on potential adverse effects. Consult the Liverpool COVID-19 Drug Interactions website or the Ontario COVID-19 Science Advisory Table for monitoring guidance and dose adjustment information if needed.[i]		
Anticoagulants • Warfarin **Anti-infective agents** • Cobicistat or ritonavir-boosted antiretrovirals • Isavuconazole • Posaconazole • Voriconazole **BPH medications** • Doxazosin • Terazosin **Diabetes medications** • Glyburide	**Cardiovascular agents** • Amlodipine • Diltiazem • Felodipine • Nifedipine • Sacubitril • Valsartan • Verapamil **Neuropsychiatric agents** • Haloperidol • Hydroxyzine • Mirtazapine • Risperidone • Ziprasidone • Zolpidem	**Pain medications** • Buprenorphine • Hydromorphone • Methadone • Morphine • Tramadol

[a] Reduced effectiveness of clopidogrel is likely. It may be acceptable to continue clopidogrel if the benefit of ritonavir-boosted nirmatrelvir treatment outweighs the risk of reduced clopidogrel effectiveness.

[b] For patients at very high risk of thrombosis (e.g., received a coronary stent within the past 6 weeks), consider prescribing an alternative antiplatelet (e.g., prasugrel) or an alternative COVID-19 therapy.

[c] Ritonavir-boosted nirmatrelvir may increase concentrations of some chemotherapeutic agents, leading to an increased potential for drug toxicities. Some chemotherapeutic agents may decrease the effectiveness of ritonavir-boosted nirmatrelvir. Please refer to the FDA EUA ritonavir-boosted nirmatrelvir fact sheet and the prescribing information for the chemotherapeutic agent and consult the patient's specialist provider. The University Health Network/Kingston Health Sciences Centre is an additional resource for evaluating drug-drug interactions for chemotherapeutic agents.

[d] For patients at high risk of arterial or venous thrombosis (e.g., had a stroke within the past 3 months with a CHA_2DS_2-VASc score of 7–9 or a pulmonary embolism within the past month), consult the primary or specialty provider and consider using an alternative anticoagulant or COVID-19 therapy.

[e] For lovastatin and simvastatin, withhold at least 12 hours before initiation of ritonavir-boosted nirmatrelvir, during treatment, and for 5 days after treatment completion. For atorvastatin and rosuvastatin, withhold at the beginning of treatment with ritonavir-boosted nirmatrelvir and resume after completion of the 5-day course. If withholding a statin is not clinically appropriate (e.g., the patient had a recent myocardial infarction), the doses of atorvastatin and rosuvastatin can be adjusted and continued, and lovastatin and simvastatin should be switched to an alternative statin.

[f] Consult a patient's specialist providers before coadministering these immunosuppressants and ritonavir-boosted nirmatrelvir. These immunosuppressants have significant drug-drug interaction potential with ritonavir, and close monitoring may not be feasible. Alternative COVID-19 therapy may need to be considered. See the American Society of Transplantation statement for more information.

[g] Abrupt discontinuation or rapid dose reduction of benzodiazepines may precipitate an acute withdrawal reaction.[2] The risk is greatest for patients who have been using high doses of benzodiazepines over an extended period.

[h] For patients with severe hepatic or renal impairment, coadministration of colchicine and ritonavir-boosted nirmatrelvir is **contraindicated** due to the potential for serious or life-threatening reactions.

[i] For medications not included on the Liverpool COVID-19 Drug Interactions website or the Ontario COVID-19 Science Advisory Table, refer to the medication's FDA label for information on coadministration with ritonavir or other strong CYP3A4 and/or P-gp inhibitors.

Key: BPH = benign prostatic hyperplasia; CHA_2DS_2-VASc = congestive heart failure, hypertension, age, diabetes, stroke, vascular disease; CYP = cytochrome P450; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; P-gp = P-glycoprotein

References

1. Stader F, Khoo S, Stoeckle M, et al. Stopping lopinavir/ritonavir in COVID-19 patients: duration of the drug interacting effect. *J Antimicrob Chemother*. 2020;75(10):3084-3086. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32556272.
2. Food and Drug Administration. FDA requiring Boxed Warning updated to improve safe use of benzodiazepine drug class. 2020. Available at: https://www.fda.gov/media/142368/download.